

### Remarks

#### *1. Status of the Application*

Claims 21 and 31 are objected to as allegedly being directed to non-elected subject matter.

The title of the application was objected to for allegedly not being descriptive of the invention to which the claims are directed.

Claims 20-32, 69 and 70 stand rejected under 35 U.S.C §112, second paragraph, for allegedly being indefinite and lacking proper antecedent basis.

Claims 20-32, 69 and 70 stand rejected under 35 U.S.C. §103(a) for allegedly being obvious in view of Goodacre (Goodacre et al., "Correction of Mass Spectral Drift Using Artificial Neural Networks," *Anal. Chem.*, **68**: 271-280, 1996), Sockalingum (Sockalingum et al., "FT-IR Spectroscopy as an Emerging Method for Rapid Characterization of Microorganisms," *Cellular and Molecular Biology*, **44**: 261-269, 1998), and Cano (Cano et al., U.S. Pat. No. 5,593,883).

#### *2. Support for Claim Amendments*

Amendments to claim 20 are supported throughout the application. In particular, amendments to claim 20 are supported, for example, at page 6, lines 22-23, where the application states that "[e]nvironmental factors include stimuli that affect the metabolic state of an organism."

Additional support for the amendments to claim 20 may be found, for example, from page 16, line 27 to page 17, line 10, where the application states:

The relationship of a microorganism's fingerprint spectrum in a first environment to its fingerprint spectrum in a second environment may be applied to transform the microorganism's fingerprint spectrum in the first environment to its fingerprint spectrum in the second environment and vice versa. Because metabolically similar microorganisms undergo similar changes in response to a change in environment, the relationship derived for a first microorganism between two environments may be applied to successfully transform the spectra of other metabolically similar microorganisms between two identical or similar environments. Therefore, in certain examples, methods of compensating for environmental drift in fingerprint spectra are disclosed. In one embodiment, the fingerprint spectra of one or more microorganisms obtained from two environments are used to compensate for environmentally induced drift in the fingerprint spectra of other metabolically similar microorganisms between the two environments [underlining added for emphasis].

As stated at page 6, lines 21-22, "Environmental factors [are] the chemical and physical parameters that characterize an environment." Thus, changes in environment are characterized by changes in environmental factors.

Claims 23, 25, 29, 30, 31 and 70 were amended solely to be consistent with and derive proper antecedent basis from amended claim 20.

Support for amendments to claim 26 may be found from page 42, line 23, to page 43, line 5, where successful compensation of environmental drift in the fingerprint spectrum of one microorganism (*A. hydrophilia*) is demonstrated using a relationship derived for a second metabolically similar microorganism (*E. coli*). Here the microorganisms are in the same class of physiologically similar bacteria (gram negative enterobacters) but are in different genera, namely, *Escherichia* and *Aeromonas*.

Amendments to claim 27 are supported at page 44, lines 19-21 where the application states that "a particularly convenient (although not exclusive) indication that a microorganism is probably is physiologically or metabolically similar is that it is in the same genus (without necessarily being the same species) [emphasis added]."

Amendments to claim 28 may be found from page 44, line 22 to page 45, line 9 where the application discusses identification of metabolically similar *E. coli* strains (same species but different strains) based on the changes in their fingerprint spectra in response to changes in environment. Since the fingerprint spectra of one microorganisms in two different environments may be used to provide a relationships that may be used to compensate for environmental drift in the fingerprint spectra of other, metabolically similar microorganisms (page 17, lines 3-5), the use of a metabolically similar microorganism of the same species but different strain to provide the relationship is clearly disclosed by the application.

Support for new claim 72 may be found, for example, from page 16, line 27 to page 17, line 10, where the application states:

The relationship of a microorganism's fingerprint spectrum in a first environment to its fingerprint spectrum in a second environment may be applied to transform the microorganism's fingerprint spectrum in the first environment to its fingerprint spectrum in the second environment and vice versa. Because metabolically similar microorganisms undergo similar changes in response to a change in environment, the relationship derived for a first microorganism between two environments may be applied to successfully transform the spectra of other metabolically similar microorganisms between two identical or similar environments. Therefore, in certain examples, methods of compensating for

environmental drift in fingerprint spectra are disclosed. In one embodiment, the fingerprint spectra of one or more microorganisms obtained from two environments are used to compensate for environmentally induced drift in the fingerprint spectra of other metabolically similar microorganisms between the two environments [underlining added for emphasis].

Additional support for new claim 74 is found on page 6, lines 17-28, where “environment” is defined as the chemical and physical surroundings of an organism and “environmental factors” are defined as the chemical and physical parameters that characterize an environment. Environmental factors include “stimuli that affect the metabolic state of an organism.”

Support for new claim 73 may be found on page 10, lines 4-23.

Support for new claims 74 and 75 may be found on 20, lines 6-8, and at page 27, lines 14-26.

Support for new claim 76 may be found in Examples 2-5 from page 29 to page 52. For example, from page 30, line 21 to page 32, line 9, an ion-by-ion correction algorithm for pyrolysis mass spectra is shown. Claim 76 also is supported by original claim 25.

Support for new claim 77 may be found from page 42, line 23, to page 43, line 5.

Support for new claim 78 may be found at page 44, lines 19-21.

Support for new claim 79 may be found from page 44, line 22 to page 45, line 9.

Support for new claim 80 may be, for example, in Example 8, at page 57, lines 5-6, and in original claim 32.

### 3. *Objections to the Claims and Specification*

Claims 21 and 31 were objected to for allegedly being directed to non-elected subject matter. Applicants traverse the objections to claims 21 and 31.

The examiner states that claim 21 is directed to non-elected subject matter because it explicitly states that the environmental factor that is varied according to claim 21 is the growth medium. The claim has apparently been withdrawn on the presumption that the generic base claim 20 is not allowable. However, as noted below, a *prima facie* case of obviousness has not been established with respect to claim 20. Claim 20 is allowable, and claim 21 should not be withdrawn, because the culture conditions are one of the environmental conditions that affect the metabolic state of the organism as in claim 20.

Applicants elected temperature as the environmental condition (factor) in Paper No. 7, filed May 6, 2003. Claim 31 states that “the first and second sets of environmental factors comprise the same batch of the same growth medium and the environmental factors differ in at least one parameter selected from the group consisting of temperature, pressure, exposure to light, and exposure to gases.” Thus, claim 31 clearly reads on the elected species of temperature as the environmental factor, and not on the growth medium being the environmental factor, since it states that the growth medium is not varied. Applicants respectfully request withdrawal of the objection to claim 31 for allegedly being withdrawn to non-elected subject matter, particularly in view of the allowability of base claim 20.

The Office action objected to the title of the invention for allegedly not being descriptive of the invention to which the claims are directed. The title of the application has been amended to recite “DRIFT COMPENSATION METHOD FOR FINGERPRINT SPECTRA.” Since the preamble of independent claim 20 recites “[a] method for compensating for drift in fingerprint spectra,” the title is descriptive of the invention to which the claims are directed, and the objection to the title should be withdrawn.

Claims 33 -38, 67 and 68 were also withdrawn from consideration, however they should be considered with the pending claims because they are directed to detecting differences between the fingerprint spectra of microorganisms grown on different culture media. Since different culture media are within the scope of “environmental factors” that affect the metabolic state of the organisms, claims 33-38 should not be withdrawn. This is particularly illustrated by the allowability of base claim 20 and linking claim 21.

*4. Rejections under 35 U.S.C. §112, second paragraph*

**Claims 20-32, 69 and 70** were rejected for allegedly being indefinite for being directed to a method for compensating drift in fingerprint spectra while reciting steps for culturing, measuring, detecting and using the differences. Applicants traverse this rejection for the reasons that follow.

Independent claim 20 has been amended to clearly recite steps that achieve the stated preamble goal, which goal also has been added to the body of the claim for clarity. How the steps recited in claim 20 accomplish the preamble goal of compensating for drift in fingerprint spectra is thoroughly and clearly explained throughout the application. For example, at page 15, lines 1-5, the application states:

In one aspect of the disclosure, methods of compensating for changes in the fingerprint spectra of microorganisms that are due to changes in the microorganism's environment are disclosed. These methods are based in part on the similar fingerprint spectra of metabolically similar microorganisms under similar environmental conditions and the similar changes observed in the fingerprint spectra of metabolically similar microorganisms in response to similar changes in environmental conditions.

From page 16, line 27 to page 17, line 5, the application states:

The relationship of a microorganism's fingerprint spectrum in a first environment to its fingerprint spectrum in a second environment may be applied to transform the microorganism's fingerprint spectrum in the first environment to its fingerprint spectrum in the second environment and vice versa. Because metabolically similar microorganisms undergo similar changes in response to a change in environment, the relationship derived for a first microorganism between two environments may be applied to successfully transform the spectra of other metabolically similar microorganisms between two identical or similar environments.

A simplified example of how the relationship derived between the fingerprint spectra of one microorganism in two different environments may be used to correct for environmental drift in a second, metabolically similar microorganism is provided in FIG. 1, which is discussed from page 29, line 1 to page 31, line 26.

Definiteness of claim language must be analyzed not in a vacuum, but in light of: (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the art (MPEP 2173.02). Here, claim 20 is definite at least in view of the content of the application, which provides numerous descriptions and examples of how the steps recited in the claim are used to achieve compensation for drift in fingerprint spectra due to changes in environmental factors. Therefore, the rejection of claim 20 for allegedly being indefinite should be withdrawn, and applicants request such action. Likewise, claims 21-32, 69 and 70, which depend from claim 20, are definite and applicants respectfully request that the rejections of these claims also be withdrawn.

**Claims 20-32, 69 and 70** stand rejected for allegedly being indefinite for failing to have antecedent basis for the feature of "a second set of environmental factors," which is recited in independent claim 20. The phrase itself ("a second set of environmental factors") demonstrates that proper antecedent basis is present. Nonetheless, claim 20 has been amended to affirmatively recite a step of "obtaining a fingerprint spectrum of the second microorganism cultured under a

second set of environmental factors.” This amendment has been made solely for clarity and to further prosecution. The rejections of dependent claims 21-32, 69 and 70 under 35 U.S.C. §112, second paragraph, also should be withdrawn.

**Claims 20-32, 69 and 70** were rejected as allegedly being indefinite for reciting the term “interest,” or depending from a claim that recites the same. Claims 20, 23, 25-29 and 70 are amended to replace the term “microorganism of interest” with the term “first microorganism.” Therefore, claims 20-32, 69 and 70 are clear and definite and the rejections should be withdrawn. Applicants respectfully request such action.

**Claim 29** was rejected for allegedly being indefinite for reciting the term “closest.” The term “closest” is part of the phrase “closest in canonical variate or principal component space,” and would not be read in isolation by one skilled in the art. Read in its entirety, the phrase is clear, especially when considered in view of the specification. As stated on page 16, lines 11-17:

In one disclosed embodiment, the fingerprint spectra of two or more microorganisms from each of two or more environments are analyzed by statistical pattern recognition and represented in canonical variate (CV) and/or principal component (PC) space. Each fingerprint spectrum is described by a set of coordinates in CV and PC space. Proximity of spectra in CV or PC space is indicative of similar fingerprint spectra and also of metabolic similarity if the spectra are for microorganisms from the same or similar environments.

On page 26, lines 18-22, the application states that “[s]ince proximity in canonical variate (CV) or principal component (PC) space is indicative of metabolic similarity, the metabolic similarity group representative that exhibits a fingerprint spectrum falling closest to the unknown’s fingerprint spectrum in such spaces may be used as the transformation basis microorganism.”

FIG. 4, discussed from page 39, line 20 to page 40, line 9, is an example of a 2-D CV score plot showing the locations of the fingerprint spectra of four microorganisms. It is clear from this figure that one skilled in the art could readily determine, for example, that the spectra obtained for *E. coli* (denoted as A in FIG. 4) are closest to the spectra for *A. hydrophila* (denoted as C in FIG. 4). These two organisms are both gram negative enterobacters, and proximity in the CV space is a reflection of their metabolic similarity. Thus, in view of the extensive discussion of proximity of spectra in CV or PC space and its relation to metabolic similarity, the meaning of “closest in canonical variate or principal component space” is definite in view of the specification. The rejection of claim 29 under 35 U.S.C. §112, second paragraph, should be withdrawn, and Applicants request such action.

5. *Rejections under 35 U.S.C. §103*

Claims 20-32, 69 and 70 stand rejected under 35 U.S.C. §103(a) for allegedly being obvious in view of Goodacre, Sockalingum and Cano. Applicants traverse these rejections, and respectfully request that the rejections be withdrawn and claims 20-32, 69 and 70 be allowed.

The Office action does not present a *prima facie* case of obviousness for claims 20-32, 69 and 70. A *prima facie* case of obviousness requires that there be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (MPEP 2143). A *prima facie* case of obviousness also requires a reasonable expectation of success and requires that the reference(s) teach all of the features of the claim (MPEP 2143.03). Here, a *prima facie* case of obviousness for claims 20-32, 69 and 70 is not provided by the Office action for at least the reasons that the cited references do not teach or suggest all of the features of the claims, and no motivation or suggestion to make the combinations of references exists.

As stated in the Background section of the application at page 2, lines 5-7, “[i]rreproducibility of spectral data due to instrumental and environmental sources makes it difficult to classify or identify microorganisms based on fingerprint spectral patterns” (emphasis added). Claims 20-32, 69 and 70 (as amended), and new claims 71-80, are directed to methods for compensating for drift in fingerprint spectra due to differences in environmental factors (or differences in environment) that affect the metabolic state of organisms. In contrast, the Goodacre reference teaches compensation for instrumental drift between measurements when the environmental conditions that metabolically affect the organism are maintained the same. (See page 274, the second, fifth and seventh full paragraphs). The Sockalingum reference does not teach or suggest any method for compensating for drift in fingerprint spectra either due to differences in instrumental or to environmental conditions. Rather, Sockalingum teaches only that “by standardizing growth conditions and instrumental parameters, IR spectra of intact bacterial cells can be reproducibly measured (page 268, emphasis added).” In other words, the Sockalingum reference teaches that both instrumental and environmental factors should be kept the same. The Cano reference does not teach or suggest fingerprint spectra, let alone any method for compensating for either type of drift in fingerprint spectra. Therefore, none of the references cited in the Office action address or provide a solution to the problem solved by the methods of claims 20-32 and 69-80, namely compensation for drift in fingerprint spectra where differences

exist in environmental factors (or in environment) that affect the metabolic state of microorganisms.

Claim 20 is not obvious in view of the cited references because no single, cited reference or any combination of the cited references (Goodacre, Sockalingum and Cano) teaches all of the features of claim 20. For example, as stated above, no cited reference or combination thereof teaches or suggests a method for compensating for drift due to differences in environmental factors that affect the metabolic state of a microorganism ("environment" and "environmental factors" are defined on page 6, lines 17-28, of the present application). Furthermore, none of the references teach or suggest a second, metabolically similar microorganism employed in a method for compensating for such differences in environmental factors. Nor do any of the references teach or suggest deriving a relationship between fingerprint spectra for the second microorganism cultured under first and second sets of environmental factors where the first and second sets of environmental factors are different and affect the metabolic state of the first and second microorganisms. In addition, none of the references teach or suggest applying the relationship derived for the second microorganism to transform the fingerprint spectrum of the first microorganism under the first set of environmental factors to an expected fingerprint spectrum for the first microorganism under the second set of environmental factors that is compensated for drift due to the differences in the first and second sets of environmental factors that affect the metabolic state of the first microorganism. Thus, a *prima facie* case of obviousness is not presented by the Office action because all of the features of claim 20 are not taught or suggested by the cited references. The rejection of claim 20 under 35 U.S.C. §103(a) should be withdrawn, and claim 20 should be allowed.

Even if the cited references taught all of the features of claim 20, a *prima facie* case of obviousness would not be established by the Office action because no motivation or suggestion exists to make the combination of references that allegedly renders claim 20 obvious. For example, Goodacre does not teach or suggest drift due to changes in environmental factors. Rather, Goodacre teaches only instrumental drift (see, for example, the Abstract, the bottom of the left column of page 280 where Goodacre states "[i]t was therefore evident that this lack of long-term reproducibility was due to instrumental drift," and the right column of page 280 where Goodacre states "[i]n conclusion, neural networks can be used to successfully to correct for instrumental drift.")). Therefore, claim 20 cannot be considered *prima facie* obvious in view of Goodacre because the modification of the method of Goodacre proposed by the Office action (to

correct for environmental drift) would change the principle of operation (correction for instrumental drift) of Goodacre (MPEP 2143.01). Moreover, Goodacre is addressing a different problem (instrumental drift) than is addressed in claim 20; references that do not even appreciate the problem being solved can not be said to suggest the claimed solution.

In addition, one of ordinary skill in the art would not be motivated to make a combination of Goodacre with Sockalingum to arrive at a method for correcting for drift due to changes in environmental factors. Sockalingum does not teach or suggest any method for correcting for environmental or instrumental drift in fingerprint spectra obtained for microbes cultured under and measured under different conditions. Rather, Sockalingum suggests only that “[b]y standardizing growth conditions and instrumental parameters, IR spectra of intact bacterial cells can be reproducibly measured” (page 268). With regard to standardization of instrumental parameters, Goodacre states in the right column of page 272 that “[u]nfortunately, this procedure does not compensate for all the instrumental drift, and additional methods need to be sought.” Thus, one of ordinary skill in the art would be discouraged from making (rather than motivated to make) a combination of Sockalingum with Goodacre to arrive at the method of claim 20, even if the combination taught all of the features of claim 20.

With regard to Cano, applicants submit that one of ordinary skill in the art would not be motivated to make a combination of either Goodacre or Sockalingum with Cano, at least for the reason that Cano does not relate to fingerprint spectra and correction thereof. To the contrary, Cano relates to isolation of bacteria fossilized in amber, and thus appears to be non-analogous art.

In summary, the Office action uses hindsight reconstruction, guided by the applicants’ own disclosure, to arrive at the combination of Goodacre, Sockalingum and Cano alleged to render claim 20 obvious. Hindsight reconstruction does not establish motivation at the time the invention was made [MPEP 2145 (X)(A)].

Claims 21-32, 69 and 70 are not obvious in view of Goodacre, Sockalingum and Cano for at least the reasons set forth for claim 20 from which they all depend. A *prima facie* case of obviousness is not presented by the Office action and the rejections of claim 21-32, 69 and 70 under 35 U.S.C. §103(a) should be withdrawn.

Furthermore, with respect to claims 26-28, no cited reference teaches or suggests deriving a relationship between spectra of a second metabolically similar microorganisms and applying

such a relationship to compensate for drift in the fingerprint spectrum of a first microorganism where the first and second microorganisms are from different genera, species or strains.

Applicants request withdrawal of the obviousness rejections to claims 21-32, 69 and 70 and allowance thereof.

New claims 71-80 are also directed to a method of compensating for environmentally induced drift in fingerprint spectra due to differences in environment that affect the metabolic state of an organism. As already noted, the cited references disclose methods of compensating for instrumental drift. These references do not even disclose an appreciation of the problem being solved, much less could they be said to suggest the claimed solution. The references do not establish a prima facie case of obviousness with respect to claims 71-80, and they are therefore allowable.

6. *Conclusion*

Applicants request reconsideration of the rejections, and submit that all pending claims are in condition for allowance. If any issues remain before a Notice of Allowance is issued, the Examiner is invited to telephone the undersigned patent attorney at the telephone number provided below.

Respectfully submitted,

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